Allergen Control in the Prevention and Management of Allergic Disease

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CONTENTS

SUMMARY OF IMPORTANT CONCEPTS

>> Exposure of individuals with established allergic disease to high levels of sensitizing allergens causes exacerbation of symptoms and worsening of the underlying inflammatory process

>> Complete cessation of exposure *early* in the natural history of the disease may lead to improvements in disease control

>> Single allergen avoidance measures are ineffective: use a comprehensive environmental control regimen aims to achieve a complete cessation of exposure, or as great a reduction in personal exposure as possible

>> Tailor the intervention to the patient's sensitization and exposure status. If unable to assess the exposure, use the level of allergen-specific IgE antibodies or the size of skin test wheal as an indicator

>> Within the context of the prevention of allergic disease, no single primary prevention strategy will be applicable to the whole population, but only to individuals within the population having a particular susceptibility

>> The concept of blanket advice aimed at the whole population needs to be replaced by individualized measures targeting those with specific susceptibilities who will benefit from a particular intervention

INTRODUCTION

The rationale for the use of environmental control in the management and prevention of allergic disease is based on the following findings:

- Sensitization to inhalant allergens is a major risk factor for asthma, rhinitis, and eczema.[1]
- Exposure of individuals with established allergic disease to high levels of sensitizing allergens causes exacerbation of symptoms and worsening of the underlying inflammatory process.[2–7]
- Complete cessation of exposure leads to the improvement in disease control, e.g.:
  - patients with seasonal allergic rhinitis have no symptoms in the absence of exposure to pollen
  - removal of atopic asthmatics into the low-allergen environment (hospitals[8] or high-altitude sanatoria[9,10]) may improve markers of asthma severity.
- Within the context of occupational allergic disease, where identification and complete avoidance of the offending allergen is feasible, cessation of exposure may be associated with a dramatic improvement in symptoms, and sometimes cure.

However, the occupational asthma model also suggests that only complete cessation of exposure *early* in the natural history of the disease will result in the resolution of symptoms; if the exposure continues for a longer period, removal from exposure may not result in symptomatic improvement (i.e., asthma becomes a self-perpetuating process, and even complete cessation of exposure to the allergen that caused it fails to affect disease progression and severity). The fact that the duration of this 'window of opportunity' within which the removal from exposure is effective appears to differ markedly between different individuals adds another level of complexity. Thus, the finding that high allergen exposure appears to contribute to the chronicity and severity of asthma does not translate directly into the effectiveness of environmental control in either treatment or prevention of disease.

All the above indirectly suggest that important principles of environmental control should:

- aim to achieve a major, if not complete cessation of exposure
- commence the intervention early in the natural history of the disease.

Table 82.1 Differences in the aerodynamic properties between house dust mite and cockroach and pet allergens

Allergen	Particle size	Airborne level	
House dust mite Cockroach	Large particles >10 µm diameter (>90%)	**Undisturbed** Undetectable with conventional assays	**Disturbed** Detectable after vigorous disturbance; settle down quickly
Cat Dog	Larger particles >5 µm (~75%) Small particles <5 µm (~25%)	**Homes with animal** Detectable in all homes. Levels 4–5 times higher with animal in the room	**Homes without animal** Detectable even without artificial disturbance

The application of effective control measures which can ensure that a low-allergen environment is achieved and maintained over a prolonged period, and identification of patients who may benefit from such intervention as early in the natural history of the disease as possible, should be the cornerstones of any potentially clinically successful environmental intervention strategy.

ENVIRONMENTAL CONTROL MEASURES

The differences in aerodynamic characteristics and distribution between various allergens have to be taken into account when designing effective methods to reduce personal exposure (Table 82.1).[11] The majority of mite and cockroach allergens are contained within relatively large particles (>10 µm diameter), and are consequently detectable in the air only after vigorous artificial disturbance. In contrast, a significant portion of airborne cat and dog allergens is carried on small particles (<5 µm diameter); airborne pet allergens are thus readily measured in houses with and without pets, and in public buildings.[12] It is likely that this may partly account for the difference in the clinical presentation of allergic asthma: whereas mite- and cockroach-sensitized asthmatics are usually unaware of the relationship between exposure to the sensitizing allergen and their symptoms, cat- or dog-allergic patients often develop wheezing/cough within minutes of entering a home with a pet (owing to the inhalation of relatively large amount of allergen carried on small particles which penetrate deep into their respiratory tract). Application of this information to environmental control measures is important, suggesting, for example, that air filtration units will have little effect on personal exposure to mite or cockroach, but may be useful in removing airborne pet allergens.

MEASURES TO REDUCE DUST MITE ALLERGENS

Reduction of mites and mite allergens in the home can be achieved by a number of measures, depending on the site of contamination (Table 82.2).[11]

Bed and bedding

The most effective measure to reduce allergen exposure in bed is to cover the mattress, duvet, and pillows with casings that are impermeable to mite allergens. Covers made of finely woven fabrics are the most effective solution.[13] Because allergens can accumulate in exposed bedding, it should be washed regularly (e.g., approximately once a week). Low-temperature washing removes allergen, but dust mites can survive it; therefore, if possible, the bedding should be washed in a hot cycle (>55°C) in order to kill the mites.

Carpets and upholstered furnishings

Ideally, carpets should be removed and replaced by hard flooring (e.g., wood or linoleum). If carpets remain in place, several methods have been suggested for reducing mite allergen levels (e.g., exposing carpets to direct strong sunlight, steam cleaning, use of acaricides or tannic acid, freezing with liquid nitrogen, etc.). However, these methods are only partially effective. Allergen reduction in upholstered furniture poses a particular problem. One approach is to have furnishings designed with an impermeable barrier below the fabric cover, or to use leather covers.

Other sources of mite allergen exposure

Fabric curtains should be replaced with Venetian blinds; freezing of soft toys kills mites, after which toys should be washed to remove allergens and dead mites.

Controlling humidity

As relatively high levels of humidity are required for mite survival and growth, reducing humidity may be used to control mite populations in the whole dwelling. However, reducing the relative humidity of the indoor air alone may not be sufficient to effectively reduce humidity in mite microhabitats (e.g., in the middle of a mattress, or deep within carpets).[14,15] Furthermore, this approach depends critically on the local climate and housing design. For example, central mechanical ventilation heat recovery units are effective at reducing indoor humidity in geographical areas where outdoor humidity is low and home insulation is good, but have not proved effective in areas where outdoor humidity is high and homes are poorly insulated. The effectiveness of portable dehumidifiers also depends on the type of climate and housing.

Clearly, a major reduction in personal exposure can only be achieved by a comprehensive strategy combining the most appropriate measures applicable to individual patients and households and a particular geographical area; simple, single measures are unlikely to achieve the desired effect. A stringent environmental control regime combining a number of the above measures can achieve and maintain a low-allergen environment over a prolonged period,[16] but such an approach may be costly and at least some patients may consider it unacceptable.

PET ALLERGEN AVOIDANCE MEASURES

The only way to effectively reduce exposure to cat or dog allergens is not to have animals in the home.[11] Even after permanent removal of an animal, it can take many months for the allergen levels in the reservoirs in the home to fall.[17] However, despite advice by health professionals, many pet-sensitized individuals with allergic disease who experience symptoms decide to continue to live with their animal.

Attempt to control pet allergen levels with pet in situ

Air cleaning units with high-efficiency particulate arrest (HEPA) filters can reduce the airborne concentration of cat and dog allergens. However, although measurements of their effectiveness under experimental conditions suggest a substantial reduction in airborne allergen levels,[18] field studies using measurements of personal inhaled allergen exposure are far less convincing.[19]

Several studies have investigated the effect of pet washing on allergen levels. A reduction in airborne cat allergens was reported following washing of one cat weekly over a 4-week period,[20] and a similar but short-lived reduction was confirmed in a later study.[21] Washing dogs reduces the levels of allergen in fur and dander samples, but levels return to the starting values within days, suggesting that washing needs to be done a minimum of twice a week to be effective.[22] However, it is unlikely that a modest reduction in allergen exposure achieved by pet washing would be sufficient to translate into a clinical benefit.

In the experimental chamber, vacuum cleaners with built-in HEPA filters and double-thickness bags do not leak pet allergens. However, a real-life study using intranasal air samplers to monitor personal exposure during vacuum cleaning has recently demonstrated up to a five-fold

Table 82.2 Practical measures for reducing house dust mite, pet, fungal, and cockroach allergen levels

House dust mite
Beds and bedding Encase mattress, pillow, and quilt in allergen-impermeable covers (preferably finely woven fabric) Wash all bedding weekly. Use hot cycle (55–60°C) if possible
Replace carpets with hard flooring (e.g. linoleum or wood)
Minimize upholstered furniture/replace with leather furniture
Replace curtains with blinds
Minimize dust-accumulating objects; keep in closed cupboards
Remove soft toys (if impossible, hot wash/freeze soft toys)
Reduce indoor humidity if possible
Cat/dog
Remove animal from the home
Fungi
Reduce indoor humidity if possible
HEPA air filters in main living areas and bedrooms
Fungicides on heavily contaminated surfaces
Minimize upholstered furniture
Replace carpets with hard flooring (e.g. linoleum or wood)
Ensure regular inspection of heating and air conditioning units to prevent contamination
Cockroaches
Remove food and water sources
Use suitable pesticide in bait form
Remove all dead carcasses and frass
Wash down all surfaces, floors, and walls with detergent
Seal cracks in walls and plaster work to reduce further access
Wash all bedding, clothing, and curtains

increase in the amount of cat allergen inhaled while using brand-new high-efficiency vacuum cleaners,[23] suggesting that data obtained in experimental chamber studies alone are insufficient to justify recommending high-efficiency vacuum cleaners to allergy sufferers.

Given the relative ineffectiveness of the measures to control pet allergen levels with the pet in situ, removal remains the only effective advice to patients with pet allergy who experience symptoms on exposure.

COCKROACH ALLERGEN REDUCTION

Physical and chemical procedures can be used to control cockroach populations in infested houses.[24–26] Identification of species, food and water sources, and hiding places is helpful. Sealing cracks and holes in plasterwork and floors can restrict cockroach access.

Several pesticides are available, in either gel or bait form. Household cleaning is an essential adjunct to successful allergen removal. Before applying insecticide, general cleaning should remove all possible food sources, and further cleaning should be delayed for a week to avoid removing insecticides.

Allergen is likely to be left adherent to walls, floors, kitchen surfaces, cupboards, appliances, and woodwork, and these must be scrubbed with water and detergent. Contaminated bedding, clothing, and curtains must be washed. Successful treatment reduces exposure in approximately 2 weeks, has maximal effect within 1 month, and will keep populations under control for up to 6 months.

ENVIRONMENTAL CONTROL IN THE MANAGEMENT OF ALLERGIC DISEASE

Attempts to replicate the clinical benefits of allergen avoidance suggested by the studies carried out at high-altitude sanatoria or hospitals by using environmental control measures in patients' homes have provided conflicting results.[11, 27–32] Thus, the effectiveness of environmental manipulation remains controversial. It has to be emphasized that the controversy is not whether allergen avoidance works – it clearly does, and the complete absence of exposure usually results in complete remission of some symptoms (e.g., seasonal allergic rhinitis) and improvement in others (e.g., asthma),[28] as demonstrated earlier in this chapter. The practical questions that are not yet fully resolved are how to achieve a sufficient reduction in personal inhaled allergen exposure and how to identify patients who will benefit from effective intervention.

MITE ALLERGEN AVOIDANCE

The measures mentioned above can be used to reduce mite allergens in the home. However, the evidence is equivocal as to whether their use has an impact on asthma or rhinitis in real life.

Systematic reviews

A recent update of the Cochrane meta-analysis reported no effect from the interventions and concluded that current methods of mite allergen avoidance should not be recommended to mite-sensitive asthmatics (Table 82.3).[33] This meta-analysis comprised 49 studies, with a total of 2733 patients (literature search current as of June 2004), with more than doubling in the number of patients since the previous version.[34] The authors suggested that the most plausible explanation for the lack of the clinical effect is that the environmental control methods used in the studies did not adequately reduce mite allergen levels (with the authors stressing that 'it seems inherently implausible to suggest that complete removal of a major provoking agent would be ineffective').[33] Furthermore, they emphasized that mite-sensitive asthmatics are usually also sensitized to other allergens, raising the question whether focusing on one allergen is the right approach to environmental control.

Further recent review of the clinical trials registered by the Cochrane Collaboration and Cochrane Airways Group attempted to study the effect of dehumidification of the home environment on asthma control (searches current as of October 2005).[35] However, only one trial comparing mechanical ventilation with or without high-efficiency vacuum cleaners met the inclusion criteria.[36] The trial did not show any clinical benefit to asthmatics, but the study was of an open design and the sample size was small, thereby rendering the findings inconclusive.

Studies in adult asthmatics

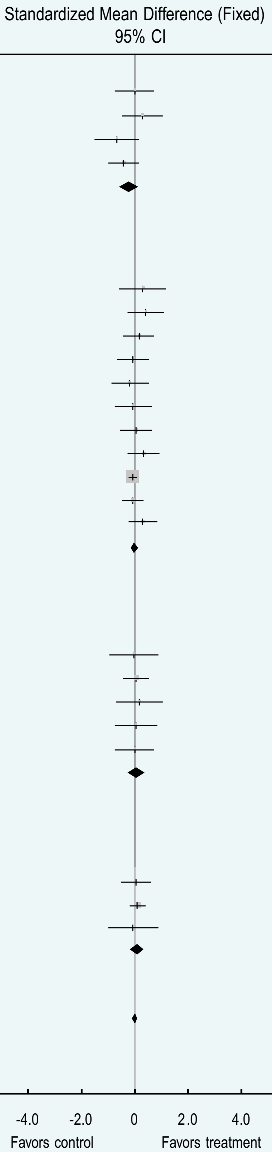
Three studies investigating mite avoidance in the treatment of asthma in adults which demonstrated a clinical benefit have been much cited as a proof that avoidance should be a part of the management of mite-sensitive patients.[37–39] However, these studies were of a very different design, with a total of only 98 patients in all three studies. In 1986, Walshaw and Evans[37] reported a small improvement in the peak expiratory flow rate (PEFR) and bronchial hyperresponsiveness (BHR) as a result of a multifaceted intervention which successfully reduced mite exposure (involving plastic mattress encasings, linoleum bedroom floor coverings, or regular vacuuming and a washing and cleaning regime over a 1-year period). In a three-way study of air cleaners and bed coverings in allergic adults with asthma, van der Heide et al demonstrated a small improvement in BHR in the group randomized to receive both the active air cleaners and allergen-impermeable covers after 6 months.[38] A small study investigating the use of active heat-steam treatment in homes with or without the use of a special ventilation system reported a sustained reduction in allergen levels in all the study participants and a significant improvement in BHR.[39]

In contrast, by far the largest randomized double-blind, placebo-controlled trial assessing the effectiveness of mite-impermeable bed covers as a single intervention, involving over 1000 adults with physician-diagnosed asthma using inhaled corticosteroids (ICS), found no benefits of the intervention in any of the primary or secondary outcome measures (morning PEFR during the first 6 months, the proportion of patients able to discontinue inhaled steroids during the second 6 months of the study, symptom scores, quality of life, etc.).[40] The patients in this study were selected irrespective of allergen sensitization and mite exposure. However, two-thirds had positive mite-specific IgE and approximately one in four beds had very high mite allergen levels (>10 μg/g of major mite allergen Der p 1). Post-hoc analysis of the subgroup of 130 patients with high mite-specific IgE (= 10 kU_A/L) and high baseline mite allergen exposure (>10 μg/g Der p 1 in mattress dust) did not demonstrate any differences in any of the outcomes between the active and the placebo groups. This was confirmed by a smaller study which recruited 55 adult patients with asthma who were sensitized to mite (mite-specific IgE >0.7 kU_A/L) and

Table 82.3 Comparison of house dust mite reduction versus control, outcome morning peak expiratory flow rate. Reproduced from Gøtzsche PC, Johansen HK. House dust mite control measures for asthma. *Cochrane Database of Systematic Reviews* 2008, Issue 2. Art. No.: CD001187, with permission, Copyright, Cochrane Collaboration.

Review: House dust mite control measures for asthma
Comparison: 01 House dust mite reduction versus control
Outcome: 05 PEFR morning (Peak Expiratory Flow Rate)

Study	Treatment N	Mean (SD)	Control N	Mean (SD)	Weight (%)	Standardized Mean Difference (Fixed) 95% CI
01 Chemical methods						
Bahir 1997	13	262.00 (82.00)	17	262.00 (82.00)	1.9	0.0 [-0.72, 0.72]
Chang 1996	12	411.00 (75.00)	14	383.00 (100.00)	1.6	0.30 [-0.47, 1.08]
Dietemann 1993	11	67.88 (11.28)	12	75.37 (10.46)	1.4	-0.66 [-1.51, 0.18]
Reiser 1990	23	92.00 (20.00)	23	100.00 (18.00)	2.9	-0.41 [-1.00, 0.17]
Subtotal (95% CI)	59		66		7.8	-0.21 [-0.56, 0.15]
Test for heterogeneity chi-square=3.58 df=3 p=0.31 I² =16.2%						
Test for overall effect z=1.14 p=0.3						
02 Physical methods - parallel group studies						
Cinti 1996	10	98.20 (22.70)	10	91.80 (15.80)	1.3	0.31 [-0.57, 1.20]
Fang 2001	19	349.00 (96.00)	16	304.00 (117.00)	2.2	0.41 [-0.26, 1.09]
Halken 2003	26	358.00 (96.00)	21	342.00 (86.00)	3.0	0.17 [-0.40, 0.75]
Lee 2003	22	88.60 (13.66)	20	89.43 (17.33)	2.7	-0.05 [-0.66, 0.55]
Luczynska 2003	16	367.00 (156.00)	15	388.00 (75.00)	2.0	-0.17 [-0.87, 0.54]
Rijssenbeek 2002	16	435.00 (115.00)	14	440.00 (115.00)	1.9	-0.04 [-0.76, 0.68]
Sheikh 2002	23	16.38 (25.62)	20	13.68 (43.14)	2.7	0.08 [-0.52, 0.68]
Walshaw 1986	22	407.00 (112.00)	20	369.00 (114.00)	2.7	0.33 [-0.28, 0.94]
Woodcock 2003	313	429.30 (91.70)	315	436.20 (88.80)	40.3	-0.08 [-0.23, 0.08]
de Vries 2007	47	457.00 (145.00)	45	464.00 (111.00)	5.9	-0.05 [-0.46, 0.36]
van den Bemt 2004	26	431.00 (115.00)	26	395.00 (109.00)	3.3	0.32 [-0.23, 0.86]
Subtotal (95% CI)	540		522		68.0	0.00 [-0.12, 0.12]
Test for heterogeneity chi-square=5.99 df=10 p=0.82 I² =0.0%						
Test for overall effect z=0.00 p=1						
03 Physical methods - crossover studies						
Antonicelli 1991	9	443.00 (106.00)	9	445.00 (117.00)	1.2	-0.02 [-0.94, 0.91]
Burr 1976	32	335.00 (111.00)	32	329.00 (118.00)	4.1	0.05 [-0.44, 0.54]
Mitchell 1980	10	67.00 (15.00)	10	64.30 (12.70)	1.3	0.19 [-0.69, 1.06]
Warburton 1994	12	350.00 (101.00)	12	344.00 (97.00)	1.5	0.06 [-0.74, 0.86]
Warner 1993	14	232.60 (88.00)	14	231.30 (97.00)	1.8	0.01 [-0.73, 0.75]
Subtotal (95% CI)	77		77		9.9	0.06 [-0.26, 0.37]
Test for heterogeneity chi-square=0.12 df=4 p=1.00 I² =0.0%						
Test for overall effect z=0.34 p=0.7						
04 Combination methods						
Carswell 1996	23	99.60 (17.80)	26	98.90 (14.50)	3.1	0.04 [-0.52, 0.60]
Cloosterman 1999	76	544.00 (132.00)	81	529.00 (126.00)	10.1	0.12 [-0.20, 0.43]
Dorward 1988	9	388.00 (106.00)	9	392.00 (71.00)	1.2	-0.04 [-0.97, 0.88]
Subtotal (95% CI)	108		116		14.4	0.09 [-0.18, 0.35]
Test for heterogeneity chi-square=0.13 df=2 p=0.94 I² =0.0%						
Test for overall effect z=0.65 p=0.5						
Total (95% CI)	784		781		100.0	0.00 [-0.10, 0.10]
Test for heterogeneity chi-square=11.66 df=22 p=0.96 I² =0.0%						
Test for overall effect z=0.03 p=1						



exposed to high levels of dust mite allergen in their mattresses (Der p 1>2 µg/g); again, there was no effect of allergen-impermeable encasings on any of the outcomes (PEFR, asthma symptoms, and medication).[41] These two trials demonstrated convincingly that a single intervention with allergen-impermeable encasings for the mattress, duvet, and pillows is ineffective in the long-term management of asthma in adults, even in individuals who are highly allergic to dust mite *and* exposed to high levels of mite allergens (the subpopulation of adult asthmatics in whom this type of intervention would be expected to have a beneficial effect).

Two further recent double-blind, randomized, controlled studies were carried out in the Netherlands, investigating the effectiveness of mite-impermeable bed covers. The larger of the two (involving 224 mite-sensitized patients with asthma and/or rhinitis and/or eczema) failed to show any effect of the intervention on quality of life.[42] A small study in 52 mite-sensitized asthmatic patients (aged 12–60 years) demonstrated an improvement in PEFR in the active compared to the placebo group, despite a very short intervention period (9 weeks).[43]

Studies in asthmatic children

Several studies have indicated that simple environmental control interventions which included mattress encasings, either alone or in combination with other mite avoidance measures (such as the use of acaricides and washing instructions for bedding), may improve airway reactivity,[44] lung function,[45] or reduce acute emergency room visits due to asthma[46] among mite-sensitized asthmatic children.

A recent study in Denmark recruited 60 mite-sensitized children, with physician-diagnosed asthma and a positive specific dust mite bronchial challenge, who were exposed to high levels of mite allergen in their beds (mattress Der p 1 >2 μg/g). Importantly, pet-sensitized pet owners were excluded.[47] The intervention consisted of polyurethane casings applied to the mattress and pillows, and advice to families to wash blankets or duvets every 3 months. The primary outcome measure was the need for asthma medication, which was titrated to the lowest possible dose of inhaled steroid at 3 monthly visits. The steroid dose was safely reduced by approximately 50% in the active group, and no effect was observed in children in the control group. The beneficial effect was not apparent until the casings had been in place for 6 months, but was maintained to 12 months.[47] There was no difference between groups in the secondary outcome measures (PEFR and dose of mite allergen provoking a positive challenge).

By far the largest study of the effectiveness of environmental control in children (the Inner-City Asthma Study) adopted a wide-ranging, comprehensive environmental intervention.[48] A total of 937 children aged 5–11 years with physician-diagnosed, poorly controlled asthma and at least one positive skin test were recruited from seven inner-city areas of the USA with high levels of poverty (more than half of the households had an annual income of less than $15 000). Despite having moderate/severe asthma, with either a hospital admission or two unscheduled visits to an emergency room or a physician in the preceding 6 months, less than half of the subjects were on anti-inflammatory agents.

The home environment was evaluated at the start of the study (including measurement of indoor allergens), and the intervention was tailored to the child's sensitization and exposure status. The comprehensive environmental control regime focused on the education of the parent/carer, and included advice on the reduction of passive smoke exposure when appropriate. Mattress and pillow casings and a high-filtration vacuum cleaner were supplied to all homes. Further products required for the tailored intervention (e.g., a HEPA air filter for the reduction in passive smoke exposure) were supplied free of charge. Owing to the complex nature of the intervention, no attempt was made to introduce placebo devices into control homes.

Children in the intervention group had significantly fewer days with asthma symptoms than did the controls; this effect was apparent within 2 months of starting the study, and was sustained throughout the 2-year period.[48] The number of emergency room visits was also reduced during the intervention year, with a number of other secondary outcome measures showing either a statistically significant improvement or a trend towards improvement in the active compared to the control group. Statistical modeling indicated that, for mite and cockroach allergen, the increase in symptom-free days was seen predominantly in children with larger (>50%) reductions in home allergen levels.[48]

This important study demonstrated that allergen levels can be reduced in poor, inner-city homes, and also estimated the size of the potential beneficial effect: a multifaceted environmental intervention costing approximately $2000 per child was associated with an additional 34 symptom-free days over a 2-year period, which was estimated to be cost-effective.[49]

Systematic reviews and studies in patients with rhinitis

A Cochrane systematic review of mite avoidance measures in the management of perennial allergic rhinitis published in 2001 reported no beneficial effect of physical or chemical intervention, concluding that there was little evidence that a reduction in mite exposure will lead to a sustained improvement in disease outcome.[50] However, only four small trials satisfied the inclusion criteria, all of which were judged to be of poor quality. Thus, at the time when the systemic review was carried out, published trials had been small and of poor methodological quality, making it impossible to make any definitive recommendations on the role of mite avoidance measures in the management of mite-sensitive perennial allergic rhinitis.[50]

Subsequent to this systematic review, the results of by far the largest randomized, double-blind placebo-controlled study of environmental control measures in patients with perennial allergic rhinitis became available.[51] A total of 279 mite-sensitized subjects aged 8–50 years with perennial rhinitis and a positive nasal challenge test to mite extract were randomized to receive either active or placebo covers for pillows, duvets, and mattress, with the primary outcome measure being symptom scores. The active covers reduced mite allergen levels collected from the mattress to approximately 30% of the baseline, whereas the placebo covers had no effect. Similar to most other intervention studies in allergic diseases, both groups reported a marked decrease in symptom scores during the 12-month follow-up period. However, there was no beneficial effect of the intervention, with no difference between the groups in any of the outcome measures.[51]

Studies in patients with eczema

There are as yet no systematic reviews assessing the effect of mite avoidance measures in patients with eczema. Apart from the previously quoted study investigating the effect of mite-impermeable casings on the quality of life of patients with asthma and/or rhinitis and/or eczema,[42] the most recent study on mite avoidance in the management of patients with eczema included 86 mite-allergic patients aged 8–50 years.[52] There were no significant differences in any of the clinical parameters between the active group (patients using mite-proof encasings for 1 year) and the control groups, despite significant reductions in mite exposure. Another small study of a similar design in 20 adults, with intervention comprising the use of mite-impermeable casings and acaricides, also failed to show any improvement in disease activity.[53] In contrast, an earlier study in which half of the study population were children, with a more

comprehensive environmental intervention which included a combination of bed covers, acaricides, and high-filtration vacuum cleaners for 6 months, demonstrated a significantly greater improvement in the severity score and area affected by eczema in the active compared to the control group.[54]

PET ALLERGEN AVOIDANCE

Based on clinical experience and observational studies,[55] it is universally accepted that there should be a significant clinical improvement associated with the absence of contact with the sensitizing pet in cat- or dog-allergic patients. It is also clear that a double-blind, randomized study of pet removal from the home is not feasible. Thus, with respect to the appropriate advice to pet-sensitized pet owners who experience symptoms upon exposure, the advice to remove the pet will always be based upon common sense, rather than the evidence obtained from rigorous trials.

There have been several attempts to study the effect of cat and dog allergen avoidance with the pet in the home. A total of three studies have addressed the effects of pet allergen control measures in pet-sensitized owners. Two showed small improvements in asthma-related outcomes,[56,57] but one did not.[58] However, the number of subjects was small and larger studies will be needed before definitive recommendations can be made.

Systematic review

A recent systematic review by the Cochrane Airways Group emphasized the paucity of evidence on the clinical effectiveness of pet allergen avoidance.[59] The review aimed to determine the clinical efficacy of pet allergen control measures in the homes of patients with pet-allergic asthma (literature search current as of September 2005), assessing only randomized controlled trials that compared an active intervention with control. However, as only a very limited amount of data was available, no meta-analysis was possible. Only two small, previously mentioned studies (22 and 35 participants, respectively) met the inclusion criteria for the analysis (both investigating the effectiveness of air filtration units).[57,58] The review concluded that both studies reported no significant differences between the active intervention and control on the primary and secondary outcomes. The authors concluded that the available trials were too small to provide unequivocal evidence for or against the use of air filtration units in the management of pet-allergic asthma.[59] Furthermore, no trials of other allergen reduction measures (e.g., pet washing or pet removal) were identified.

IDENTIFICATION OF PATIENTS WHO ARE LIKELY TO BENEFIT FROM AN EFFECTIVE INTERVENTION

In clinical practice, as in the most of the studies of environmental control, allergic sensitization is usually considered only as a dichotomous variable – i.e., individuals are assigned as either sensitized or not, based on arbitrary cut-off points on either skin tests or measurement of specific serum IgE. However, some recent findings indicate that in the context of respiratory illness, IgE-mediated sensitization should not be considered as a simple all-or-nothing phenomenon, as the probability of wheezing and reduced lung function in childhood appears to increase with increasing specific IgE antibody levels.[60] Application of these findings in the context of environmental control is unclear. It is possible that the level of specific IgE antibodies or the size of skin test wheal may better identify those individuals who are more likely to benefit from effective environmental intervention, compared to the mere presence or absence of sensitization.

ENVIRONMENTAL CONTROL IN THE PREVENTION OF ALLERGIC DISEASE

The consistent finding of an association between allergic sensitization and childhood asthma raises the question as to whether environmental control with successful reduction in exposure to allergens early in life can reduce the risk of subsequent development of sensitization and/or symptoms of allergic disease. This question is being addressed by several 'primary prevention' studies. However, these studies are by design long term, and will take many years to report definitive findings. This topic has been a subject of several recent review articles.[61,62]

Seven ongoing studies which have published results to date are described in more detail below. All of these primary prevention studies have of necessity focused on children at high risk of developing allergic disease. However, the definition of 'high risk' differed between studies (e.g., both parents atopic, single parent atopic, mother with asthma, etc.). Furthermore, it is important to emphasize that all of the studies used different environmental control approaches and were of a different design (e.g., four of the studies included a dietary intervention in addition to the environmental control). In addition, the studies used different definitions of primary outcomes and assessed those at different ages. Therefore, the results between the studies are not directly comparable.

ISLE OF WIGHT STUDY

This was the first study to implement an intervention designed to reduce exposure to allergens as part of a primary prevention program in 120 children (58 intervention, 62 control).[63–66] The intervention included avoidance of both food and dust mite allergens up to age 9 months. Mothers who were breastfeeding their children were asked to avoid allergenic foods, and these foods were not introduced into the infant's diet until after 9 months of age. Infants who were not breastfed were given a hydrolyzed formula. Environmental control consisted of the application of acaricide to carpets and upholstered furniture. Infants in both groups slept on polyvinyl-covered mattresses with a vented head area. Mite allergen levels at age 9 months were lower in the active than in the control group. However, it is worth noting that even after the intervention, mite allergen levels were still higher than the baseline levels seen in most other studies.

Children were reviewed at age 1, 2, 4, and 8 years. A reduction in sensitization and wheeze was reported at 1 year,[63] but at ages 2[64] and 4 years[65] differences in respiratory symptoms failed to reach statistical significance. At age 8 years, sensitization to mite was reduced by more than 50% in the active group, despite only modest reductions in mite allergen levels.[66] In the multivariate analysis, children in the active group were significantly less likely to have current wheeze, nocturnal cough, wheeze with bronchial hyperresponsiveness, and atopy.[66]

Despite modest reductions in mite allergen levels, the combined intervention used in this study has resulted in a marked reduction in

important clinical signs and symptoms suggestive of childhood asthma. However, owing to the study design it is impossible to determine which part of the intervention was responsible for the effect.

CANADIAN PRIMARY PREVENTION STUDY

In the Canadian Primary Prevention Study (CaPPS), the multifaceted intervention included measures to reduce exposure to both inhalant and food allergens.[67,68] Compliance with mattress casings and acaricides (applied by the study nurses) was excellent. Mite allergens were significantly reduced in the parental bed throughout the study. However, for the child's mattress, levels were low in both groups after birth. Despite advice, there was no reduction in the use of carpets or pet ownership.

At age 2 years the authors assigned the participants as having asthma on an a priori definition based on frequency and duration of episodes of cough or wheeze, breathlessness, and asthma medication usage.[67] Using these descriptions, there was a significant reduction in probable asthma in the active group. In addition, there was a reduction in rhinitis without colds. At age 7 years, 380 children returned for further assessment. The prevalence of physician-diagnosed asthma was significantly lower in the intervention group than in the control group (14.9% vs 23.0%).[68] The prevalence of allergic rhinitis, eczema, atopy, and bronchial hyperresponsiveness was not significantly different between the two groups. Thus, in this study the multifaceted intervention program appeared effective in reducing the prevalence of asthma in high-risk children at 7 years of age.[68]

STUDY ON THE PREVENTION OF ALLERGY IN CHILDREN IN EUROPE

The Study on the Prevention of Allergy in Children in Europe (SPACE) included newborn children from Austria, Germany, and the UK.[69,70] The recruitment methods varied slightly between centers, and 696 children were enrolled in the three countries. The multifaceted intervention was directed towards both inhalant and food allergens. Mite avoidance focused on the infants' beds, with the application of mattress covers (unless they were vinyl), but allergen levels were not measured. Mothers were advised to breastfeed children, and hypoallergenic formula was recommended as an alternative (Austria and Germany, but not the UK). Parents were advised to delay the introduction of potentially allergenic foods. Compliance with the measures was reported to be good. At age 1 year there was a reduction in sensitization to mites, but no difference in the proportion of children who had ever wheezed (21% in both groups).[69]

More than 80% of the children were reviewed at the age of 24 months. No differences were found between the control and intervention group in the prevalence of mite sensitization (8.4% control vs 6.1% intervention) or the development of respiratory symptoms (wheezing 10.3% vs 10.7%, nocturnal cough 12.5% vs 12.5%) or allergic diseases (asthma 3.5% vs 5.1%, eczema 20.0% vs 19.6%, rhinitis 28.9% vs 25.8%).[70] In this study, mite avoidance did not have a protective effect on the development of sensitization or symptomatic allergy in children at age 2 years.

THE CHILDHOOD ASTHMA PREVENTION STUDY

The Childhood Asthma Prevention Study (CAPS) is a multicenter, parallel-group, randomized controlled trial in Sydney, Australia.[71–73] Families at risk (without a cat in home) were randomized into one of four study groups (mite avoidance with placebo dietary intervention, $n = 155$; mite avoidance with active dietary intervention, $n = 153$; active dietary intervention alone, no mite avoidance, $n = 159$; placebo dietary intervention, no mite avoidance, $n = 149$). Although a significant reduction in mite levels was achieved in the mite intervention group, these levels were much higher than pre-intervention levels in other studies (owing to the climatic conditions, which facilitate growth of the mite population). The dietary intervention consisted of omega-3 fatty acid supplementation, and was not designed to reduce exposure to potentially allergenic foods but to increase dietary omega-3 fatty acids from age 6 months.

Clinical outcome data at age 18 months were available for 554 children.[71] Despite the fact that a significant proportion of children had become sensitized (~20%), there was no difference in rates of sensitization between the groups. Children in the active dietary intervention group had significantly less wheeze than those on the placebo supplements (42.8% vs 52.6%), and most other wheeze indicators were lower in this group but did not all reach statistical significance. At age 3 years there was a significant reduction in sensitization to house dust mite in the active mite allergen avoidance group, but no significant differences in wheeze were found with either intervention.[72]

Of 616 children randomized, 516 were evaluated at age 5.[73] The mite avoidance intervention resulted in a 61% reduction in allergen concentrations in the child's bed, but no differences between the randomized groups were observed in the prevalence of asthma, wheeze, or atopy. The prevalence of eczema was higher in the active mite avoidance group (26% vs 19%).[73] The ratio of omega-6 to omega-3 fatty acids in plasma was lower in the active diet group, but the prevalence of asthma, wheezing, eczema, or atopy did not differ between the diet groups. Thus, in the Australian study dust mite avoidance measures and dietary fatty acid modification during infancy and early childhood did not prevent the onset of asthma, eczema, or atopy in high-risk children by age 5 years.

THE PRIMARY PREVENTION OF ASTHMA IN CHILDREN STUDY

In The Primary Prevention of Asthma in Children (PREVASC) study in the Netherlands, a total of 476 children were recruited during the prenatal period and randomized to either a control group (receiving usual care) or an intervention group in which families received instruction from nurses on how to reduce exposure of newborns to mite, pet and food allergens, and passive smoking. At 2 years of age, the intervention group ($n = 222$) appeared to have fewer asthma-like symptoms, including wheezing, shortness of breath, and night-time cough, than the control group ($n = 221$).[74] However, no significant differences in total or specific IgE were found between the groups.[74] Furthermore, the incidence of asthma-like symptoms during the first 2 years of life was similar in both groups; however, subanalysis revealed a significant reduction in the intervention group in females, but not in the males. Thus, the intervention used in this study was not effective in reducing asthma-like symptoms in high-risk children during the first 2 years of life, although some modest effect was observed at age 2.[74]

PREVENTION AND INCIDENCE OF ASTHMA AND MITE ALLERGY STUDY

The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study is a multicenter, population-based cohort study of over 4000 children in the Netherlands.[75,76] Nested within this cohort is an intervention

study among 810 high-risk infants who were randomly allocated to receive either active mite-proof casings for the mattress and pillows of the parental and infant beds or cotton placebo casings in a double-blind manner. No casings were supplied for the duvet or blankets, and advice was given to the active group to wash bedding regularly at more than 60°C. Baseline mite allergens levels were low in both groups. One year after the introduction of the intervention, allergen levels were significantly lower in the active than in the control group, but with little change in the absolute value. Over the first year, levels of mite allergen in the child's mattress increased significantly more in the control than in the active group.

At age 2 years, the only significant difference between groups in the clinical outcomes was a reduction in night-time cough without a cold in the active group. There was no difference in levels of total serum IgE or atopy at age 1 year.[75] At age 4, sensitization and allergic symptoms were similar in both groups.[76] Thus, in this study there was no effect of mite allergen-impermeable mattress covers on sensitization and symptoms suggestive of allergic disease at age 4 years.

MANCHESTER ASTHMA AND ALLERGY STUDY

The Manchester Asthma and Allergy Study (MAAS) is a whole-population birth cohort study of more than 1000 children, with a nested intervention study in the high-risk group. Participants were recruited from the antenatal clinics, where prospective parents were skin tested and answered a questionnaire regarding symptoms and diagnoses of allergic disease. Only children with two atopic parents who had no pets in their home were randomly allocated before birth to a stringent environmental control (n = 145) or normal regime (n = 146).[77,78] The comprehensive environmental control regime included the fitting of mite-proof casings to the parental mattress, duvet, and pillows by 16th week of pregnancy, advice to wash bedding weekly at over 55°C, supply of a high-filtration vacuum cleaner, and Acarosan to apply to dust reservoirs with high mite allergen levels. Just before the birth of the child, custom-made cot and carrycot mattresses (made of allergen-impermeable fabric) were supplied to the family, carpets were removed from the nursery, and a vinyl cushion floor was fitted. A hot washable toy was also supplied. No attempt was made to introduce placebo devices into the control homes.

A significant and sustained reduction in exposure to mite, cat, and dog allergens was observed in the homes of children in the active group. At age 1 year there was slightly more atopy in the intervention group than in the control group (17% vs 14%), but this did not reach statistical significance.[77] Asthma-like symptoms were consistently lower in the intervention than in the control group, and this reached statistical significance for attacks of severe wheeze with shortness of breath, prescribed medication for wheezy attacks, and wheeze after playing or exertion. No difference between the groups was seen for eczema.

Counterintuitively, at age 3 years children in the intervention group were significantly *more* frequently sensitized to dust mite than were controls (risk ratio = 2.85).[78] However, lung function (assessed by the measurement of specific airway resistance) was markedly and significantly better among children in the intervention group. Furthermore, the authors suggested that the improvement in lung function in the environmental intervention group occurred between birth and age 3 years as a consequence of some aspect of the environmental control regime, as there was no difference between the groups in infant lung function at age 4 weeks.[78] Thus, in MAAS, stringent environmental control was associated with an increased risk of mite sensitization, but better lung function at age 3 years.

CONCLUSIONS

Although the general consensus is that environmental control should lead to an improvement in symptoms in susceptible patients with allergic disease, there is little evidence to support the use of simple physical or chemical methods as single interventions to control dust mite or pet allergen levels (e.g., mattress casings, acaricides, or HEPA filters). Whereas it remains possible that a multifaceted intervention in carefully selected patients could have some effect, this has not so far been addressed in an adequately designed study in adult asthma; thus, there is currently inadequate evidence to advise this as a strategy to this age group.

In contrast, several small trials of allergen-impermeable bed casings as a single intervention in asthmatic children reported benefits, as did a large study of a more comprehensive environmental intervention in children living in poor-quality housing. The reasons for the apparent differences in response between adults and children are not clear, but the situation may be analogous to that observed with occupational asthma, where prompt removal from exposure to a sensitizing agent is associated with a better long-term outcome than removal after prolonged exposure.

For rhinitis and eczema, the most recent well-designed studies on single mite avoidance measures failed to demonstrate a clear clinical benefit.

Until there is unequivocal evidence for all age groups and all allergens, the pragmatic approach to environmental control should use the following:

- Single avoidance measures are ineffective: use a comprehensive environmental control regime aiming to achieve a complete cessation of exposure, or as great a reduction in personal exposure as possible.
- Tailor the intervention to the patient's sensitization and exposure status. If unable to assess the exposure, use the level of allergen-specific IgE antibodies or the size of skin test wheal as an indicator.
- Start the intervention as early in the natural history of the disease as possible.

With respect to the use of environmental control in the prevention of allergic disease, clinical outcomes reported from different intervention studies appear inconsistent and often confusing. Ongoing prevention cohorts have provided us with a wealth of information, but much longer follow-up is required before we can be sure that the interventions do not cause any harm, and can confidently give any practical clinical advice. It is becoming clear from recent data that no single primary prevention strategy will be applicable to the whole population, but only to individuals with a particular susceptibility.[79] With respect to the advice on prevention strategies using environmental control, we need to move away from the concept of blanket advice aimed at the whole population towards individualized measures targeting those with specific susceptibilities who will benefit from a particular intervention.[80]

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